Correlating Clinical Scores with Anatomical Electrodes Locations for Assessing Deep Brain Stimulation

Florent Lalys, Claire Haegelen, Alexandre Abadie, Pierre Jannin

Correlating clinical scores with anatomical electrodes locations for assessing deep brain stimulation

Florent Lalys [1,2,3], Claire Haegelen [1,2,3,4], Alexandre Abadie [1,2,3], Pierre Jannin [1,2,3]

[1] INSERM, U746, Faculty of Medicine CS 34317, F-35043 Rennes, France
[2] INRIA, VisAGeS Unit/Project, F-35042 Rennes, France
[3] University of Rennes I, CNRS, UMR 6074, IRISA, F-35042 Rennes, France
[4] Department of Neurosurgery, Pontchaillou University Hospital, F-35043 Rennes, France

Abstract. Movement disorders in patients with Parkinson's disease may require functional surgery, when medical therapy isn't effective. In Deep Brain Stimulation (DBS), electrodes are implanted within the brain to stimulate deep structures such as SubThalamic Nucleus (STN). This paper describes successive steps for constructing digital atlases gathering patient's location of electrode contacts and clinical scores. Three motor and three neuro-psychological scores were integrated in the study. Correlations between active contacts localization and clinical data were carried out using an adapted Hierarchical Ascendant Classification and have enabled the extraction of clusters aiming to suggest optimum sites for therapeutic STN DBS. The postero-superior region has been found to be effective for motor score improvement whereas the antero-inferior region revealed noticeable neuro-psychological scores deterioration. Comparison with existing results has shown that such atlases are very promising for understanding phenomena better.

Keywords: Deep Brain Stimulation, digital atlases, subthalamic nucleus, Parkinson disease

1 Introduction

Parkinson's disease (PD) is recognized as one of the most common neurological disorders, affecting 1% of people older than 60 years. The pathology is an age-related deterioration of certain nerve systems, which affects the patient's movement, balance, and muscle control. Major symptoms are indeed characterized by abnormalities of motor functions, several of which predominate, but all do not necessarily occur in all individuals. While these symptoms related to PD can be treated with medication therapy, few patients have side effects or treatments for which it is not effective. In

such cases, Deep Brain Stimulation (DBS) [1] might be necessary, according to strict patient inclusion criteria. The target for DBS in Parkinson's disease has been moved from the ventro-lateral thalamic nucleus (Vlc) to the medial global pallidus (Gpm) and the Sub-Thalamic Nucleus (STN). Among these three deep brain structures, the STN became the mean target of high-frequency DBS in patients with PD and severe disabled symptoms [2]. Even if STN DBS has proved its efficiency for motor symptoms improvement, several studies have reported adverse-events after DBS surgery affecting cognitive functions, emotion or behavior [3,4,5]. It remains interrogations about contacts location that provide the largest motor improvement while producing the least clinical side effects.

Preoperative definition of the target is based on the relief of symptoms and results of previous implantations only. Its precise localization from patient images is unfeasible mainly due to contrast and spatial resolutions limitations. Consequently, the surgeon needs additional information and knowledge for indirect identification of such small-targeted structures. Some are explicit such as anatomical atlases adapted to the patient images thanks to image registration. Some are implicit knowledge, such as the one acquired from learning, literature, and previous surgical cases. Different strategies have recently studied methods for making explicit this implicit information and knowledge. The concept of probabilistic functional atlases has been introduced [6]. After a step of normalisation within a common space, effective contacts are linked to a large panel of parameters acquired during the various stages of the procedure. The spatial normalisation allows performing retrospective studies, where statistical techniques are used to study anatomical or functional variability between patients. Response to stimulation, electro-physiological recordings, and clinical scores related to motor or cognitive evolution are all possible information that can be integrated in such atlases [7,8,9,10]. This fusion of information permits to understand functional organization within deep brain structures that helps for the identification of the optimal zone of therapy.

As far as we know, no functional atlases were proposed yet for representing the relationships between the anatomy and a large panel of clinical scores. While most of these atlases are using a single motor score for modelling the global outcome of the patient, we proposed in this paper to extend this research by adding motor and neuropsychological scores. We thus introduce the concept of anatomo-clinical atlases and describe the methods for their computation.

2 Materials and Methods

In this study, the objective was to correlate anatomical position of electrode contacts with clinical outcomes in STN DBS. After an automatic segmentation of electrode contacts for each patient, the crucial step was to perform an accurate patient-to-template registration, allowing expressing contacts coordinates in a common reference space. Then the integration of clinical scores obtained pre and post-operatively permitted the extraction of representative anatomo-clinical clusters. We describe in this section every stage of our procedure, from the extraction of electrode's contacts to the creation of atlases.

2.1. Data

The study population consisted of 23 patients (10 women and 13 men, mean age 60 years old) with idiopathic PD who had bilateral STN DBS according to selected inclusion criteria at the University Hospital of Rennes (France). Patients had pre-operative 3-T T1-weighted MR (1 mm x 1 mm x 1 mm, Philips Medical Systems), pre and post-operative CT scans (0.44 mm x 0.44 mm x 0.6 mm in post-operative acquisitions and 0.5 mm x 0.5 mm x 0.6 mm in pre-operative acquisitions, GE Healthcare VCT 64). All images were denoised with the Non-local means algorithm [11], and a bias correction algorithm [12] based on intensity values was also applied on T1 MR images.

2.2. Contact localization and registration workflow

Electrode contacts coordinates have to be first extracted from patient's post-operative images, and then warped into a common space to perform a retrospective study for population comparison. The spatial coordinates of each electrode contact were determined based on black artefacts from CT images, corresponding to the center of the actual contact [13]. The segmentation process included an intensity threshold, a search for the artefacts, and constraints on neighborhood. An additional step of extrapolation was necessary when just two or three contacts were identified from the four (due to the resolution of the CT scan).

We then used, as a common space, a mono-subject high-resolution 3T MRI brain template, constructed and assessed in [14]. The registration workflow was described and validated within the validation part of the template in the context of DBS in [15]: the post-operative CT was first linearly registered to the pre-operative MRI. An affine MR-to-template transformation was then computed, followed by a local affine registration computed on a region of interest within deep brain structures. With this procedure the contacts positions could be precisely warp into our template.

2.3. Clinical scores

From numerous clinical scores assessed in our population, we studied UPDRS III (Unified PD Rating Scale [16], part III, taking into account akinesia, tremor, rigidity) widely used to assess bilateral motor improvement of patients, the Schwab & England [17] scale, and the Hoehn & Yahr [18] scale. We also studied 3 neuro-psychological scores that are often assessed through the STROOP score [19] that tests the global cognitive efficiency, and the verbal fluency tests [20] (both categorical and phonemic) that determine the ease with which patients can produce words. For each score, patients were tested without medication just before surgery (DBS OFF) and three months after it under stimulation (DBS ON). We took the difference between DBS ON and DBS OFF to compute a value that represents for all scores the degree of improvement or worsening of the patient.

2.4. Atlases

Atlases were computed as the 3D visualization of active contacts that are represented by a color code related to the patient clinical scores values. Due to errors or missing in report scoring, 15 patients were incorporated in the motor studies, and 22 in the neuro-psychological ones. Left and right contacts are shown on atlases. The x-axis represents the left-right direction, the y-axis represents the antero-posterior direction, and the z-axis represents the caudo-cranial direction.

2.5. Creation of clusters

After atlas construction, we performed a segmentation step with the help of non-supervised techniques. The Hierarchical Ascendant Classification (HAC) was used on clinical scores and coordinates to search homogeneous groups of patients. Feature vectors are composed of 4 features: the value of the x-axis, y-axis, z-axis, and the score value: $X = (x, y, z, Score)$. The HAC operates by successively merging pairs of existing clusters, where the next pair of clusters to be merged is chosen as the pair with the smallest distance. This linkage between clusters a and b was performed with the Ward criterion along with the weighted Euclidean distance:

$$d^2(a,b) = n_a n_b \frac{\sum_{k=1}^{M} w_k (\overline{x_{ak}} - \overline{x_{bk}})}{n_a + n_b} \quad (1)$$

where $\overline{x_a} = \frac{1}{n_a} \sum_{i=1}^{n_a} x_{ai}$ is the centroid of cluster a (resp. b), n_a (resp. n_b) is the number of objects in cluster a (resp. b), and w_k are the weights, specified by $w_1 = w_2 = w_3 = \frac{1}{12}$ and $w_4 = \frac{3}{4}$. The dendrogram was cut in order to obtain two or three clusters for each clinical score. Validation of the non-supervised classification was performed with an ANOVA test. Different clusters were computed in order to correlate clinical scores and anatomical location of electrode contacts. Compare to clustering on clinical scores only, adding the coordinates permits better definition of clusters and better appreciation of the efficiency of DBS according to contacts locations.

3 Results

For all following figures, we superimposed an ellipse to improve clinical representation and interpretation. This ellipse was extracted from the segmentation of the STN by an expert, and has sensibly the same dimension of a standard STN (10 x 6

x 3 mm). For each clinical score, analyses were made for both hemispheres, but all clusters found included same patients. This assumes a symmetry of the contact coordinates between the left and the right sides of patients.

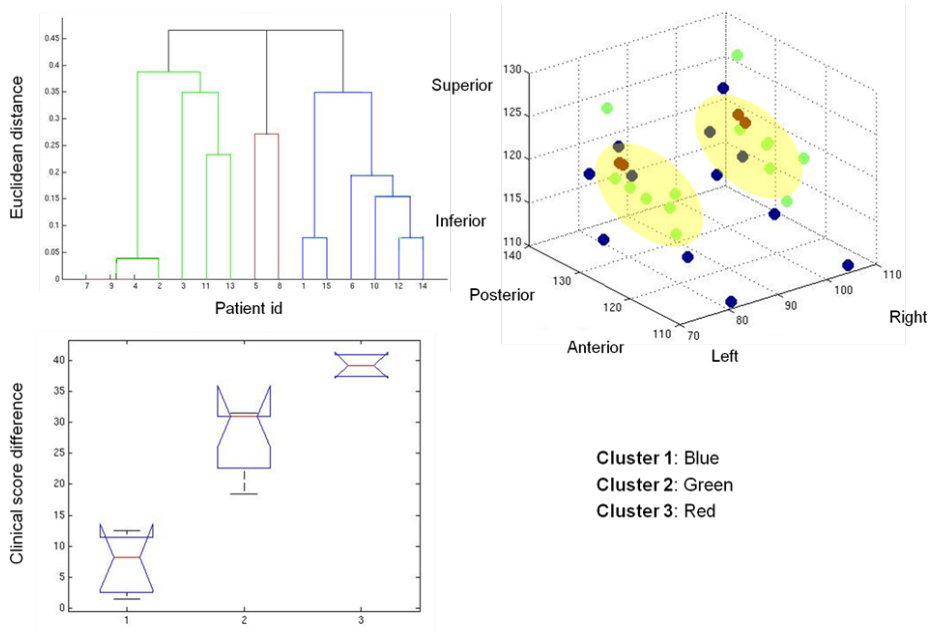

Fig. 1. UPDRS III analysis, with the dendrogram (left hemisphere), the cluster display and the ANOVA validation. Coordinates are defined in mm in the template reference space. Euclidean distances are between centroïds of clusters.

Fig. 1. shows an improvement of UPDRS III in the postero-superior region (cluster 3 in red including 2 patients), whereas the worst scores are situating mainly outside the STN and in the antero-inferior region ($p = 10^{-6}$). H&Y and S&E scores showed similar results, but with a fuzzy definition of clusters ($p = 5.10^{-2}$).

From Fig. 2., we can see a deterioration of the categorical fluency in the posterior region (green), and an improvement in the antero region (blue) ($p = 10^{-4}$). For the phonemic fluency we found a general deterioration for all patients, without apparent separation of clusters. The analysis of the STROOP score indicated score improvement in the postero-superior region, and deterioration in the antero-inferior region ($p = 10^{-5}$).

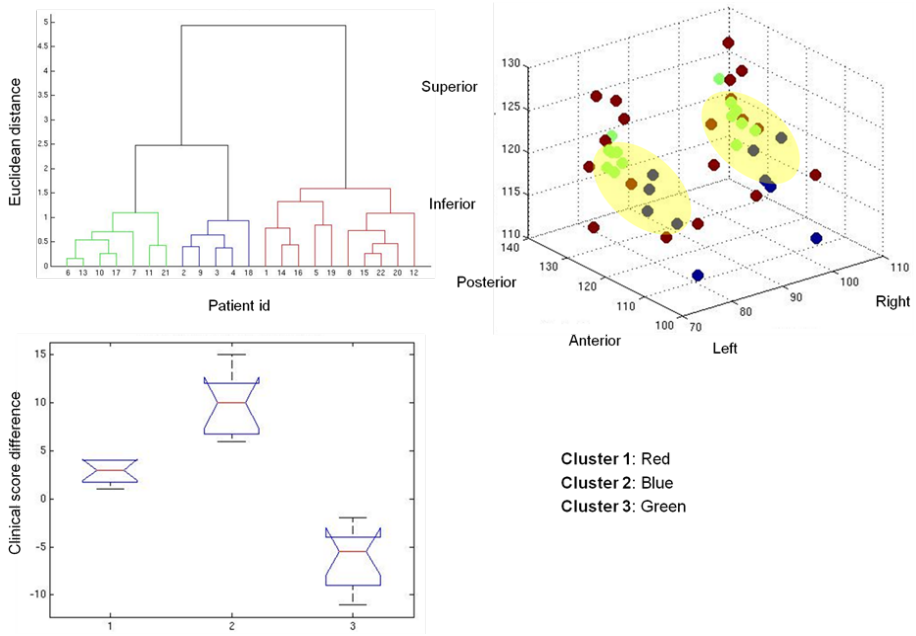

Fig. 2. Categorical fluency analysis, with the dendrogram (left side), the cluster display and the ANOVA validation. Coordinates are defined in mm in the template reference space. Euclidean distances are between centroïds of clusters.

4 Discussion

4.1. Contact localization

Using conclusions of published works on electro-magnetic contacts effects, we have modeled the signal by a point corresponding to the center of the artifact. For further developments, it will be crucial to integrate not only the real electric current that contacts emit but also the influence of stimulation on the biological tissues. Moreover, brain shift has a real impact on the final location of electrode's contacts. A full DBS modeling would integrate all of these information to be as precise as possible.

4.1. Registration workflow

Use of digitalized atlases is vital in DBS, for being able to help anatomical targeting. The impact of our high-resolution 3T MRI template on registration accuracy was significant and it has improved the registration quality around the basal ganglia area (about 0.8 mm. [10]). Such fusion of images should be taken with precaution, because differences of anatomy between each patient make difficult the representation of

contacts in a common space. Moreover, the subject used for the mono-subject template was younger than all patients, introducing a potential bias considering the differences of anatomy between the reference subject and the patients. Nevertheless, in opposition to pure histological templates made from cadaver brain, MR templates are representing correctly in vivo anatomy of the brain.

Many active contacts are situated outside the STN within atlases. It can be partially explained by the error during the warping step, but this particularity has another explanation. First, the electrical stimulation zone is in fact larger than the simple contact position, recovering a region wide enough to accept a targeting inaccuracy. Secondly, deep brain tissues and nerves are deeply inter-connected and nerves at the periphery of structures had a role on the structure itself.

4.2. Clinical scores

Retrospective studies with clinical data allowed understanding functional organization within deep brain structures. Each clinical score has permit to extract specific meaningful clusters. Motor scores were first analysed to assess the global outcome and then neuro-psychological scores have permitted to determine sites that were the cause of side-effects.

The main issue of this procedure is the incapacity to distinguish the response to the DBS stimulation of the right and left sided. Every test has been performed with both activated contacts. Separate evaluations would involve many hours without medication and stimulation in order to lose previous therapeutic and stimulation effects. In the preoperative targeting procedure, surgeons first localized the optimal target position of one side, and the target position of the other side was automatically computed with the definition of the midsagittal plane. These targets were used as an initial position that has to be refined per-operatively, but for this study we considered them symmetric which may explain some errors on the electrode position.

Because of their low granularity, values of the S&E and H&Y scales turned out to be less representative than UPDRS III. Even if results of motor scores studies were almost identical, the visualization of the atlas containing the UPDRS III shows that the postero-superior region was the most effective region for motor improvement. This follows conclusions of previously published works [10,21], and can be explained by the fact that this part of the STN (usually named the dorso-lateral part) is implicated in sensory and motor functions [22].

The STN is also subdivided into a ventromedial associative and a medial limbic territory. This subdivision explains that the antero-inferior (corresponding to the limbic territory) region has shown significant neuro-psychological side effects (deterioration of the Stroop score). This side effect is usually avoided by an implantation within the postero-superior region of the STN, but can easily appear if the contact is located not far from the antero-inferior region. Finally, the posterior region has shown a loss of categorical fluency. This last result was not surprising as the deterioration of the verbal fluency is one of the most observed side effects in STN DBS, with no real comprehension of the phenomena [23].

4.3. Clinical use

The proposed anatomo-clinical atlases have been created to provide the surgeons with an additional help for better comprehension of DBS related phenomena. It could find its application in pre-operative planning as well as for post-operative assessment. As the targeting is mainly based on surgeon's knowledge and experience, it could serve as an additional source of information obtained from retrospective studies for reducing time and improving patient outcome. The underlying challenge would be to reduce the intra-operative time required for electrode's contacts adjustment by microelectrode recordings. The actual local anaesthesia would be replaced by a general anaesthesia which would completely alter the surgical routine by reducing works of the surgical staff and improve patient's care. Alternatively, such atlases also permit to understand previous interventions which didn't give satisfactory results. In such cases, active contacts of the new patient can be warped in the common space and can be displayed.

5 Conclusion

In this paper, we focused on finding the optimum site for STN DBS by creating anatomo-clinical atlases. Such functional atlases associate anatomical position of active contacts with clinical scores for a population of cases, and are helpful for determining sites within the STN that could be the source of side effects. We showed how to extract clusters and knowledge gained from the population data based on the correlation between anatomical location of contacts and clinical data. It permits to provide the neurosurgeons with a help for targeting, but also permits to understand previous interventions which didn't give satisfactory results. This work is an example of news that can be performed in the domain, including further clinical data such as life-quality or cognitive criteria. Further studies will certainly allow learning more about DBS, better understanding of clinical side-effects and defining the optimum site for each patient according to its clinical preoperative scores.

Acknowledgments. The authors would like to acknowledge Pr. M. Vérin, Dr. S. Drapier, both neurologists from the University Hospital Of Rennes for allowing access to the clinical scores.

References

1. Benabid, AL., Krack, P., Benazzouz, A., Limousin, P., Koudsie, A., Pollak, P. Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: methodologic aspects and clinical criteria. Neurology, 55, 40-44 (2000)
2. Rodriguez-Oroz, M.C., Rodriguez, M., Guridi, J., Mewes, K., Chockkman, V., Vitek, J., DeLong, M.R., Obeso, J.A. The subthalamic nucleus in parkinson's disease: somatotopic organization and physiological. Brain, 124(9), 1777--1790 (2001)

3. Parsons, TD., Rogers, SA., Braayen, AJ., Woods, SP., Troster, AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol, 5, 578–588 (2006)
4. Biseul, I., Sauleau, P., Haegelen, C., Trebon, P., Drapier, D., Raoul, S., Drapier, S., Lallement, F., Rivier, I., Lajat, Y., Verin, M. Fear recognition is impaired by subthalamic nucleus stimulation in Parkinson's disease. Neuropsychologia, 43, 1054–1059 (2005)
5. Houeto, JL., Mesnage, V., Mallet, L., Pillon, B., Gargiulo, M., du Moncel, ST., Bonnet, AM., Pidoux, B., Dormont, D., Cornu, P., Agid, Y. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry, 72, 701-707 (2002)
6. St-Jean, P., Sadikot, AF., Collins, L., Clonda, D., Kasrai, R., Evans, AC., Peters, TM. Automated atlas integration and interactive three-dimensional visualization tools for planning and guidance in functional neurosurgery. IEEE Trans. On Med. Imaging, 17(5), 854-866 (1998)
7. D'Haese, PF., Cetinkaya, E., Konrad, PE., Kao, C., Dawant, BM. Computer-aided placement of deep brain stimulators: From planning to intraoperative. IEEE TMI, 24(11), 1469-1478 (2005)
8. D'Haese, PF., Pallavaram, S., Li, R., Remple, MS., Kao, C., Neimat, JS., Konrad, PE., Dawant, BM. CranialVault and its CRAVE tools: A clinical computer assistance system for deep brain stimulation (DBS) therapy. Med Image Anal, Ahead of print (2010)
9. Guo, T., Parrent, AG., Peters, TM. Surgical targeting accuracy analysis of six methods for subthalamic nucleus deep brain stimulation. Computer Aided Surgery, 12(6), 325-334 (2007)
10. Pallavaram, S., Dawant, BM., Remple, M., Neimat, JS., Kao, C., Konrad, PE., D'Haese, PF. Effect of brain shift on the creation of functional atlases for deep brain stimulation surgery. Int J Comp Assist Radiol Surg, 5(3), 221-228 (2009)
11. Coupe P, Yger P, Prima S, Hellier P, Kervrann C, Barillot C. An Optimized Blockwise Non Local Means Denoising Filter for 3D Magnetic Resonance Images. IEEE TMI, 24(4), 425-441 (2008)
12. Mangin, JF. Entropy minimization for automatic correction of intensity non uniformity. MMBIA '00 Proc. of the IEEE Workshop on Math. Method in Biomed. Image Analysis. Hilton Head Island, 162-169 (2000)
13. Pollo, C., Villemure, JG., Vingerhoets, F., Ghika, J., Maeder, P., Meuli, R. Magnetic resonance artefact induced by the electrode activa 3389: an in vitro and in vivo study. Acta Neurochirurgica, 146(2), 161-164 (2004)
14. Lalys, F., Haegelen, C., Ferre, JC., El-Ganaoui, O., Jannin, P. Construction and assessment of a 3T MRI brain template. NeuroImage, 49, 345-354 (2010)
15. Lalys, F., Haegelen, C., Abadie, A., Jannin, P. Post-operative assessment in Deep Brain Stimulation based on multimodal images : registration workow and validation. Proceedings of SPIE, 7261 (2009)
16. Fahn, Y., Elton, R. Unified Parkinson's disease rating scale, in Fahn S, Marsden C, Calne D, Goldstein M (eds): Recent Developments in Parkinson's Disease. 2, Florham Park, NJ: Macmillan, 153-163 (1987)
17. Schwab, RS, England, AC Jr. Projection techniques for evaluating surgery in Parkinson's Disease. 152-157 (1968)
18. Hoehn, M., Yahr, M. Parkinsonism: onset, progression and mortality. Neurology, 17 (5), 427-42 (1967)
19. Stroop, J.R. Studies of interference in serial verbal reactions. Journal of Experimental Psychology, 18, 643--661 (1935)
20. Troyer AK, Moscovitch M, Winocur G, Leach L, Freedman M, "Clustering and switching on verbal fluency tests in Alzheimer's and Parkinson's disease", J int Neuropsycholog Soc, 4(2), 137-43 (1998)

21. Lanotte, MM., Rizzone, M., Bergamasco, B., Faccani, G., Melcarne, A., Lopiano, L. Deep Brain Stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. J Neurol Neurosurg Psychiatry, 72, 53-58 (2002)
22. Theodosopoulos, P.V., Marks, W.J., Christine, C., Starr, P.A. Locations of movement-related cells in the human subthalamic nucleus in parkinson's disease. Movement disorders, 18(7), 791-798 (2003)
23. Saint-Cyr, J.A., Trépanier, L.L., Kumar, R., Lozano, A.M., Lang, A.E. Neuropsychological consequences of chronic stimulation of the subthalamic nucleus in Parkinson’s disease. Brain, 123, 2091--2108 (2000)